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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/388,899	09/02/1999	BEREND HOUWEN	10690/T/B/A	4619

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EXAMINER	
GABEL, GAILENE	
ART UNIT	PAPER NUMBER
1641	17

DATE MAILED: 08/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/388,899	HOUWEN ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 7-15* is/are rejected.

7)☒ Claim(s) *5 and 6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Amendment Entry

1. Applicant's amendment and response filed 4/7/03 in Paper No. 16 is acknowledged and has been entered. Claim 1 has been amended. Claim 15 has been added. Accordingly, claims 1-15 are pending and are under examination.

Rejections Withdrawn

Claim Rejections - 35 USC § 112

2. In light of Applicant's amendment, the rejection of claims 1-14 under 35 U.S.C. 112, second paragraph, is hereby, withdrawn.

3. In light of Applicant's argument, the rejection of claims 5-6 under 35 U.S.C. 103(a) as being unpatentable over Bowen et al. (Laboratory Hematology, 1997) in view of Gopinath et al. (Cytometry, 1997) is hereby, withdrawn.

Claim Objections

4. Claim 15 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form.

Specifically, claim 15 substantially recites the same limitation, i.e. order of procedural steps, as recited in claim 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-4 and 7-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bowen et al. (Laboratory Hematology, 1997) in view of Gopinath et al. (Cytometry, 1997) for reasons of record and reiterated as follows.

Bowen et al. teach patterns of expression of CD16 and CD11b antigens by cells in bone marrow of patients using flow cytometric monoclonal antibody-based, three color immunofluorescence technique which permits simultaneous characterization of different cell populations (see Abstract). In flow cytometric analysis studies, Bowen et al. teach aspirating a hematological sample (bone

marrow) into blood collection tubes, staining the cells using a combination of three different monoclonal antibodies, then lysing erythrocytes using Ortho Lyse. Specifically, Bowen et al. teach staining the sample with the combination of fluorescent labeled antibodies including 1) fluorescence-labeled CD45 antibody (first antibody), fluorescence isothiocyanate (FITC)-labeled CD16 antibody (second antibody), and phycoerythrin (PE)-labeled CD11b antibody (third antibody). Five parameters were measured flow cytometrically which include side angle scatter (SALS), forward angle scatter (FALS), Tri-color fluorescence intensity, FITC intensity, and PE intensity. In data analysis, a gate was set to classify immature (developing) and mature fluorescence labeled granulocytes (using fluorescence-labeled CD45 antibody) which have high side angle scatter, thus, excluding other leucocytes that are not granulocytes (blasts, monocytes, and lymphocytes) which have lower side angle scatter. From the granulocyte gate, events were also quantified in fluorescence intensity measurements of the cells labeled with FITC-labeled CD16 antibody and PE-labeled CD11b antibody (see page 294, column 1). Bowen also confirmed that peripheral blood neutrophil populations within varying maturation levels (promyelocytes, myelocytes, metamyelocytes, and band cells) are quantified within the CD11b and CD16 regions because both CD16 and CD11b normally increase during the maturation of granulocytes from promyelocytic stage to segmented neutrophil stage (see page 292, column 2, page 295, column 1, and page 296, column 1). Bowen further observed that the manual percentage of band to segmented neutrophils correlated well with CD16 expression suggesting that in the course of

granulocyte maturation, CD11b expression appears earlier and prior to the expression of CD16; therefore, anti-CD16 antibodies are more useful in defining granulocytes in later maturation stages than CD11b (see page 296, column 2). In conclusion, Bowen teach that simultaneous quantitation of SALS and fluorescent labeled monoclonal antibody binding to CD45, CD16, and CD11b define highly reproducible developmental maturation patterns of the granulocytic cell population series in flow cytometry.

Bowen et al. differ from the instant invention in failing to teach staining leucocytes after the erythrocytes are removed from the hematological sample.

Gopinath et al. teach identification of leucocytes, i.e eosinophils after lysis of whole blood samples (see Abstract). According to Gopinath, use of lysed whole blood in flow cytometry allows the study of cell surface markers such as CD45, CD16, and CD11b using antibodies to CD45, CD16, and CD11b, respectively, on leucocytic cell populations without using cell purification techniques that may affect expression of these markers. In study, Gopinath et al. teach using PE labeled anti-CD16 to distinguish neutrophils from eosinophils. According to Gopinath, CD16 is expressed uniformly in immature to mature neutrophilic stages (metamyelocyte, band, and segmented neutrophils); by contrast, eosinophils are CD16 negative (see page 313, columns 1-2).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of Gopinath in distinguishing eosinophil populations from other neutrophilic populations using a combination of angle scatter measurement and fluorescent intensity measurement of cell

surface antigens using antibodies, with the flow cytometric method of Bowen because Gopinath specifically taught that a combination of side angle scatter and fluorescence intensity measurements of specific cell surface antigens using antibodies provides for accurate isolation of eosinophils from neutrophils. One of ordinary skill in the art at the time of the instant invention would have been motivated to incorporate the teaching of Gopinath in lysing hematological samples prior to performing the flow cytometric method taught by Bowen which assesses expression of cell surface markers such as CD45, CD16, and CD11b because Gopinath specifically taught that use of lysed hematological samples, i.e. whole blood, in flow cytometry allows the study of cell surface markers on cell populations of granulocytes, lymphocytes, and monocytes without using cell purification techniques that may affect expression of these markers.

Response to Arguments

6. Applicant's arguments filed 4/7/03 have been fully considered but they are not persuasive.

A) Applicant contends that Examiner never points where Bowen et al. disclose that neutrophilic cells are classified and counted into different groups of maturation on the basis of anti-CD16 and anti-CD11b antibodies.

In response, Bowen et al. teach flow cytometric analysis of CD45, CD16, and CD11b using antibodies specific thereto in page 292, column 2, page 294, column 1, and 296, column 1 wherein fluorescence and orthogonal scatter of cells having CD24 surface antigens identifies leucocytes in bone marrow, and

cells having CD16 and CD11b have large increases in antigenic expression during granulocyte maturation stages; thus, identifying early to late granulocytic maturation stages: promyelocytic, myelocytic, and metamyelocytic stages.

B) Applicant argues that claims 1-4 and 7-15 are not suggested by the combination of Bowen et al. with Gopinath et al. because the combination fails to meet the requirements of the claimed invention, specifically claim 1.

In response, the combination of the teaching of Bowen et al. and Gopinath et al. read on the claimed invention. Specifically, Bowen et al. teach combining a hematological sample (bone marrow) with three fluorescent labeled antibodies, i.e. first, second, and third antibodies, specific for leucocytes (CD45), neutrophils, and developing or immature granulocytes (CD16 and CD11b), removing the erythrocytes using Ortho Lyse, and classifying between granulocytic groups and immature granulocytic groups using flow cytometric gating system. Gopinath et al. was incorporated thereto for the teaching of identification of leucocytes, i.e eosinophils after lysis of whole blood samples, using a combination of angle scatter and fluorescence intensity measurement. Gopinath et al. use PE labeled anti-CD16 antibody to distinguish neutrophils from eosinophils. Accordingly, claims 1-4 and 7-15, as currently recited, are suggested by the combination of Bowen et al. and Gopinath et al.

Allowable Subject Matter

7. Claims 5 and 6 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday, Tuesday, and Thursday, 5:30 AM to 2:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (703) 305-3399. The fax

phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-0169.

Christopher L. Chin

Gailene R. Gabel
Patent Examiner
Art Unit 1641

8/19/03

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
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